

P A Sobotka et al., Free Radical Biology and Med, Vol. 14, pp 643-647, 1993, reported reduced breath Pentane in Heart Failure, by the use of free radical scavengers (Pentane is produced as a by-product of lipid peroxidation). The use of the above general non-specific adsorbents ("non-specific", with respect to adsorbing specific antibodies), namely: the use, for example, of sheep anti human immunoglobulin antibody, as the adsorbent for the removal (adsorption) of auto antibodies to the  $\beta 1$  adrenergic receptor in the treatment of IDCM, will remove many of the autoantibodies that contribute to the etiology and/or pathogenesis of the disease (autoantibodies to:  $\beta 1$  adrenergic receptor, oxidized LDL, ADP-ATP carrier, alpha and beta cardiac myosin heavy chain isoform, G protein coupled receptors, heart mitochondria).

Please substitute the following paragraph for the paragraph beginning at page 20, line 17:

The devices of the present invention make possible the use of a single device having contained therein a binding compound bound to a carrier, the binding compound having affinity for a binding partner, which may later be combined by a user with one or more of a plurality of affinity binders, each of the affinity binders comprising a first portion comprising the binding partner and a second portion adapted to bind selectively with a species, the second portions of each of said affinity binders differing from each other. The generic columns can be produced and shipped without the affinity binders, and the user can easily select and bind the affinity binder to the column by passing a solution of the affinity binder through the column before it is used. Alternatively, the affinity binder or binders can be bound to the generic column prior to shipment. The binding partners are illustratively Avidin and Biotin, wherein Avidin is illustratively the binding compound, permitting the use of a single, possibly certified, Avidin column to produce columns which bind selectively to a vast number of species which are naturally present in the treated mammal, or are introduced into the mammal being treated, such as by administering the species (such as a drug) to the mammal being treated, or by self-overdose of a prescription or over-the-counter drug or of a drug of abuse, or by self

administration, accidental or deliberate, of a toxic chemical substance such as a poison. These species may also include, for example, TNF alpha, IL-6, CD3+ DR+ T cells, CD4+CD28null T cells, CD3+, CD56+, DM1, VGO1, LAK1, CRP, INF gamma, CA, NAB, CA-NAB, TGF  $\beta$ , P15E, Sialomucin, TH2 T cell epitope, tumor infiltrating lymphocyte (TIL) marker, lymphokine activated killer cell (LAK) marker, Interleukin 10 (IL-10), prostaglandin E2 (PGE2), mucin, suppressive E receptor (SER), immunosuppressive acidic protein (IAP), adhesion molecules, sR TNF alpha, sR TNF beta, sR IL-1, sR IL-2, sR IL-6, sR INF gamma, heat shock protein (HSP), antibodies to oxidized LDL (Ab-OxLDL), antibodies to HSP, CRP, triglycerides, IL-2, metalloproteinases, other proteinases, fibrinogen, creatine kinase, IL-I -Beta, IL-I-Ra, PDGF, angiotensin II, MCSF, pregnancy associated plasma protein A (PAPPA), antibodies specific to any of the following: the  $\beta$ 1 adrenergic receptor, ADP-ATP carrier, alpha cardiac myosin heavy chain isoform, beta cardiac myosin heavy chain isoform, G Protein coupled receptors, and heart mitochondria, and toxins selected from the group consisting of botulinum toxin, tetanus toxin, ricin toxin, ricin A peptide toxin, sulfur mustard toxin, and toxic metabolites thereof.

Please substitute the following paragraph for the paragraph beginning at page 49, line 16:

Removal of multiple molecular inflammatory factors (MIFs) in the treatment of AS, in particular AIS, utilizes methods and devices disclosed in U.S. Patent 6,039,946, particularly as described in col. 8 line 31 to col. 13 line 62 and in Figures 4, 5 and 6. The methods and devices are essentially similar to ~~Example 1~~ Example 76, except that multiple adsorbents are utilized, with each adsorbent being specific to or selective for each one of the MIFs. The adsorbents are incorporated in the ECA in accordance with patent 6,039,946. The preferred adsorbents are antibodies, preferably Mabs, including fragments. When an Avidin column is used, the biotinylated antibodies are bound to the Avidin as described in ~~Example 1~~ Example 76, with respect to Mab specific to IL-6: the adsorbents incorporated in the ECA can be adsorbents for any of the MIFs, including but not limited to all the MIFs described in the background

section above and to the species etiological in AS that are described in patent 6,039,946. Mabs are known to many of the MIFs and in any event can be produced by using techniques known in the art, for the production of Mabs.

Please substitute the following paragraph for the paragraph beginning at page 50, line 16:

The treatment may be utilized by itself or in addition to ECA treatment as described in ~~Examples 1 and 2~~ Examples 76 and 77. It involves the administration of antibodies, preferably Mabs, preferably chimeric or humanized and including fragments, synthetic fragments and analogs which are specific to one or more of the MIFs, for example the Mab specific to IL-6.

Please substitute the following paragraph for the paragraph beginning at page 50, line 21:

Also, in addition to ECA conventional anti inflammatory drugs, receptor antagonists and anti coagulants, for example and any other drugs used in the treatment of AS, in particular AIS, can be used in conjunction with the use of the ECA methods in all of the Examples given herein. In addition to conventional drugs, anti inflammatory cytokines, such as IL-10, TGF-Beta (K Mizzia et al., supra, M. Londei, in Encyclopedia of Immunology, I. M. Roitt and P. J. Delves Eds., Academic Press 1992, pp. 443-445), can be administered in conjunction with the treatment described in ~~Examples 1-5~~ Examples 76-77 and 79-81, or as a stand-alone treatment.

Please substitute the following paragraph for the paragraph beginning at page 51, line 4

The immunogenic MIF, is preferably administered in conjunction with an adjuvant, preferably an adjuvant known in the art ~~to~~ to be suitable for administering to humans, for example, one of the adjuvants disclosed in U.S. Patent 6,054,127. The immunogen may be incorporated in a liposome in order to increase its immunogenicity, as known in the art (G. Gregoridas, Trends in Biotechnology, Vol. 13, pp. 527-37, 1995). MIFs of MW below 10000 kD are

preferably conjugated to a suitable carrier, as known in the art, for example KLH, Albumin or peptides.

Please substitute the following paragraph for the paragraph beginning at page 51, line 13:

This method is used by itself, or in conjunction with any of the methods and devices described in ~~Examples 1-4~~ Examples 76-79 and 81. The method involves the removal by affinity adsorption, of Cellular Inflammatory Factors (CIFs). Optionally this is done by Extracorporeal treatment of, blood, plasma, or in some situations, other biological fluids, but in most applications of the method is utilized by removing blood and treating it outside the body, without the use of ECA, and returning the treated blood to the treated subject. Any one, or more of the CIFs mentioned in the background section can be removed.

Please substitute the following paragraph for the paragraph beginning at page 53, line 4:

The molecular species include autoantibodies specific to any of the following: the  $\beta_1$  Adrenergic Receptor, autoantibodies specific to oxidized LDL, ADP-ATP Carrier, alpha cardiac myosin heavy chain isoform, beta cardiac myosin heavy chain isoform, g protein coupled receptors, and heart mitochondria. The method utilizes methods and devices disclosed in U.S. Patent 6,039,946, particularly as described in col. 8, line 31 to col. 13, line 62 and in Figures 4, 5 and 6, except that one or multiple adsorbents are utilized. When more than one adsorbent are utilized, each adsorbent being specific to or selective for each one of the molecular species. The adsorbents are incorporated in the ECA in accordance with patent 6,039,946. The preferred adsorbents are the respective biotinylated antigens, to which the Autoantibodies are specific or the adsorbents can be biotinylated antiidiotypic antibodies that are specific to the respective autoantibodies. The antiidiotypic antibodies are preferably Mabs, including fragments. When an Avidin column is used, the biotinylated antigens or the biotinylated antibodies are bound to the Avidin as

described in ~~Example 1~~ Example 76, with respect to Mab specific to IL-6.

When antiidiotypic Mabs are used as the adsorbents they can be produced by using techniques known in the art, for the production of Mabs.

The parameters of ECA procedure: Flow rate, length of treatment session, will be in the range of the parameters described in Example One.